Cognitive Impairments with Space, Time & Numbers (& Maybe How to Fix Them!)

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Objects, Space & Numbers

Space and Time are very abstract concepts that have “scale” but no actual values attached to them.

- We use mental “units” to break them up meaningfully.
- We have to learn “how” much is a(n): inch/second, foot, hour.
- Numbers were invented to describe “how many” units.

What if your “mental units” don’t match parts of the real world accurately?

- Space/time estimates will be wrong, numbers won’t make sense.
- This is what I now think explains many (not all) cognitive impairments of those with 22q11.2DS.

If so, we’ll know what to fix and how. We’re (almost) ready to try!
Can We Explain the Problem?

- Focus in DS22q11.2 tends to be on “Performance IQ” visual-spatial, -constructive, numbers, math, attention

- Often called “Nonverbal Learning Disorder” (NLD)

- Just a description, but what is explanation?
  - how does “software” work, with what “data” & “hardware”

- Two Main Ideas that MIGHT explain this
  
  1. Reduced Resolution of space/time “mental units”
  2. Developmental changes in brain structure and connections
Spatiotemporal Resolution

• Representations are configurations of elements of given size, orientation, color, intensity ... 
  • digital image (picture) elements are pixels

• Size of elements (grains) is called “granularity”

• Larger, (& thus fewer) elements to represent space and time would lower resolution & impact mental computations
  • mental image is “grainer” (like digital camera)
  • so resolution of mental pictures is worse
  • discriminating requires “more difference” to be accurate
“Crowding” & Attentional Resolution

From Cavanagh, 2004
“Crowding” & Attentional Resolution

Q

2 2 Q 1 1
Reduced Space & Time Resolution
Measuring Parts of Space

Task: Press button to choose who Kermit the Frog is closer to (Miss Piggy or Fozzie Bear?)

When Kermit is not close to one end or at the center, error occurs.
Bigger “pixels” reduce spatial accuracy (resolution) when location in space is unclear (i.e. not center or ends).
Measuring Time

Duration comparison:
Judge longer of two durations:
400ms vs +/- 10ms diff. (staircase method)
Auditory & visual

From Debhané et al., 2005
Increased threshold (bigger difference) due to “bigger pixels” thus reduced resolution of mental time representations.

BUT, not everything is worse and this can guide intervention!
Spatiotemporal Attention - MOT

Ready?
Spatiotemporal Attention - MOT

MOT TouchScreen "k" Statistic - 30fps & 60fps
22q (N=10) vs Control (N=10)

Average "k" Values

Number of Targets

TD-30fps
22q-30fps
TD-60fps
22q-60fps
Comparing Quantities

Task: Choose the “bigger” of the two bars or numbers

- difference between values is varied

Much easier to confuse two values when they are “close together”

People represent quantities in mental space $(\text{small} \rightarrow \text{L A R G E})$

- smaller “distance” = less distinct
Comparing Quantities

Impairment ($\partial<5$) due to reduced resolution of mental space representations and NOT general impairment
Not Everyone is Impaired!

Two questions:
- what in mind and brain allows some kids to perform like TDs?
- can we make that happen for those who are impaired?
Navigating Space I

Orienting attention impaired in children with 22q11.2DS vs. typical children.

But we found *reacting to* a cue produced less impairment than *using one to direct search*.

This experiment has the child do every variant of interest
Steeper solid (not dashed) pink than blue slopes shows specific Endo but not Exo impairment

Impairment only in volitional not reactive search in space!

Implies differentially impaired circuits
Navigating Space to get Numbers

- Task: Say out loud, as fast as possible, how many green boxes you see

Mental pictures of 3 or fewer usually created “all at once”
But for larger sets must find and count one object at a time
- then treat all the collected parts as a whole = 7
Navigating Space to get Numbers

NO impairment with small sets but searching and counting errors when groups are large and complex - “go small”!!

TD undercounts here = 54%
22q undercounts here = 70%

[Graph showing adjusted RT (ms) for different quantities (One to Eight) with error bars. The graph compares Con RT and 22q RT with TD and 22q undercounts.]
Brain Structure & Connections

• Well-defined brain circuits typically process space/time info described in mature humans and animals.
• Many components are atypical in DS22q11.2.
• Critical ones are early-developing subcortical regions.

• Changes might create suboptimal spatiotemporal circuits.
• Output impairs typical development.
• Weaker cortical circuits for space/time/number cognition.
• Connectivity should be responsive target for intervention!
Time & Space Related Circuits
Identified in animals & humans. Midline, subcortical areas critical

From Rao et al., 2001

From Karnath et al., 2002
Gray Matter Differences

Con > 22q
- Interhemisphere
- Cerebel, Culmen
- Mid/Post. Cingulate
- Fronto-Temporal
- Thalamus, Caudate

22q > Con
- R. Insula,
- R. MFG

Simon et al. NeuroImage, 2005
Cavum Septum Pellucidum 22q11.2DS

- When 2 sides of ventricles do not grow together after infancy
- Introduced new “extreme” category of CSP >15mm length
- 80% of TD no/normal CSP
- 36% of 22q abnormal CSP
- 24% extreme
- CSP volume did not correlate with IQ
- Beaton et al., submitted

Table 1. - The frequency of CSP in children with 22q11.2DS and typically developing controls according to anteroposterior length classification scheme.

<table>
<thead>
<tr>
<th>Groups</th>
<th>None (0 mm)</th>
<th>Normal (1-4 mm)</th>
<th>Borderline (5-6 mm)</th>
<th>Abnormal (&gt;6 mm)</th>
<th>Extreme (&gt;15 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22q11.2DS (N = 45)</td>
<td>7 (15.6)</td>
<td>20 (44.4)</td>
<td>2 (4.4)</td>
<td>5 (11.1)</td>
<td>11 (24.4)</td>
</tr>
<tr>
<td>Male (N = 20)</td>
<td>2 (4.4)</td>
<td>10 (22.2)</td>
<td>2 (4.4)</td>
<td>1 (2.2)</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Female (N = 25)</td>
<td>5 (11.1)</td>
<td>10 (22.2)</td>
<td>0 (0.0)</td>
<td>4 (8.9)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>TD (N = 35)</td>
<td>15 (42.9)</td>
<td>13 (37.1)</td>
<td>4 (11.4)</td>
<td>3 (8.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Male (N = 22)</td>
<td>9 (25.7)</td>
<td>10 (28.6)</td>
<td>1 (2.9)</td>
<td>2 (5.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Female (N = 13)</td>
<td>6 (17.1)</td>
<td>3 (8.6)</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Pulvinar Measures

• New pulvinar tracing protocol using DTI overlay

accurate pulvinar measures show R. Hemi reduction

strong correlation with spatial attention performance

Shapiro et al., @ Biol. Psych., 2008
Hippocampal Changes

Measured hippocampal & amygdalar volume in 72 7-14-yr-olds

- 36 22q11.2DS, 36 TD

No differences in amygdala

Unlike Kates et al, 2006

Left, not right, hippocampal volume smaller in 22q11.2DS

- 2.31 cm³ vs 2.56 cm³, p<.01

Volume correlated differentially with IQ measures

DeBoer et al., 2007
Cerebellar Changes

- Vermis/Lobes traced from mid-sagittal slice
- Relative to controls, smaller:
  - 22q total cerebellum
  - 22q anterior lobe
  - 22q neocerebellum
  - 22q cerebellar tonsils

Bish et al., 2006

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cerebellum</th>
<th>Anterior lobule</th>
<th>Inferior posterior lobule</th>
<th>Superior posterior lobule</th>
<th>Neo-cerebellum</th>
<th>Tonsils</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS22q11.2 (N = 31)</td>
<td>1114.09 (236.55)</td>
<td>362.94 (62.36)</td>
<td>583.77 (175.1)</td>
<td>143.87 (38.95)</td>
<td>295.09 (101.49)</td>
<td>110.52 (20.24)</td>
</tr>
<tr>
<td>Controls (N = 23)</td>
<td>1359.56 (261.89)</td>
<td>430.39 (61.93)</td>
<td>722.96 (204.52)</td>
<td>171.48 (45.32)</td>
<td>379.26 (129.89)</td>
<td>128.91 (18.16)</td>
</tr>
<tr>
<td>Percentage of reduction</td>
<td>18.1*</td>
<td>15.7*</td>
<td>19.3</td>
<td>16.1</td>
<td>23.2*</td>
<td>14.3*</td>
</tr>
</tbody>
</table>

* Significant difference between groups when covarying for age, gender, and total brain volume, p < .05.
Dysconnectivity & Spatial Attention

Connectivity relates to water diffusion as white matter has high water content.

Clusters suggest different connectivity regions in 22q vs TD

- strong correlation with spatial attention

Simon et al., 2008

Axial = x (primary)
Radial = average(y+z)
FA = Axial/Total

In all clusters:
FA: 22q>TD, p<.0001
RD: TD>FA, p<.0001
Gyrification changes capture key structural/connective changes. May indicate joint impact of genetic & neuroconstructive influences.
Object Tracking Brain Differences
Summary

- New hypotheses **MAY** explain cognitive problems
- Changes can be seen in parietal & frontal network
- **BUT,** may result from problems in more basic circuits
- Not all areas of nonverbal function are impaired
  - Where they are, they are not due to general dysfunction
- So areas of strength provide:
  - Pathways to improved learning in problem areas
  - Targets for improvement by intervention on impairments
Exciting News!

- Main Research Program
  - funding for next 5 years approved in Mid Feb
  - will start July, 2009
  - plan to re-recruit previous participants still <15yrs old
  - new advanced research, first longitudinal measures
  - will provide basis for intervention design

- News on Interventions

- Clinical Support and “At-Home” Telemedicine Follow-ups
Thanks

• MOST important: Kids who participated & their families!!

• Majority of the work presented here was done by:
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